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1.	Your Reference	P59013B(GB)
2.	Patent Application number *(The Patent Office will fill in this part)*	0319119.4 14 AUG 2003
3.	Full name, address and postcode of the or each applicant *(underline all surnames)*	OPTINOSE AS Lokkaskogen 18c 0773 Oslo Norway
	Patents ADP Number *(if you know it)*	80429 05001
	If the applicant is a corporate body, give the country/state of its incorporation	Norway
4.	Title of the invention	DELIVERY DEVICES
5.	Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	FRY HEATH & SPENCE LLP The Gables Massetts Road Horley Surrey RH6 7DQ United Kingdom
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		Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
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8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* a) *any applicant named in part 3 is not an inventor; or* b) *there is an inventor who is not named as an* c) *applicant, or* d) *any named applicant is a corporate body* *(See note (d))*	Yes

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	Translations of priority documents	
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	Request for preliminary examination and search *(Patents form 9/77)*	1
	Request for substantive examination *(Patents form 10/77)*	
	Any other documents *(please specify)*	
11.	I/We request the grant of a patent on the basis of this application. Signature: Keith Bod[en]	Date: 14 August 2003
12.	Name and daytime telephone number of person to contact in the United Kingdom	Dr Keith Boden - 01293 776880

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DUPLICATE

DELIVERY DEVICES

The present invention relates to a delivery device, in particular a breath-actuated nasal delivery device, for and a method of delivering substance, in particular one of a liquid, as a suspension or solution, or a powder containing a medicament, especially systemic or topical pharmaceuticals, or a vaccine to the nasal airway of a subject.

Referring to Figure 6, the nasal airway 1 comprises the two nasal cavities separated by the nasal septum, which airway 1 includes numerous ostia, such as the paranasal sinus ostia 3 and the tubal ostia 5, and olfactory cells, and is lined by the nasal mucosa. The nasal airway 1 can communicate with the nasopharynx 7, the oral cavity 9 and the lower airway 11, with the nasal airway 1 being in selective communication with the anterior region of the nasopharynx 7 and the oral cavity 9 by opening and closing of the oropharyngeal velum 13. The velum 13, which is often referred to as the soft palate, is illustrated in solid line in the closed position, as achieved by providing a certain positive pressure in the oral cavity 9, such as achieved on exhalation through the oral cavity 9, and in dashed line in the open position.

There are many nasal conditions which require treatment. One such condition is nasal inflammation, specifically rhinitis, which can be allergic or non-allergic and is often associated with infection and prevents normal nasal function. By way of example, allergic and non-allergic inflammation of the nasal airway can typically effect between 10 and 20 % of the population, with nasal congestion of the erectile tissues of the nasal concha, lacrimation, secretion of watery mucus, sneezing and itching being the most common symptoms. As will be understood, nasal congestion impedes nasal breathing and promotes oral breathing, leading to snoring and sleep disturbance. Other nasal conditions include nasal polyps which arise from the paranasal sinuses, hypertrophic adenoids, secretory otitis media, sinus disease and reduced olfaction.

In the treatment of certain nasal conditions, the topical administration of medicaments is preferable, particularly where the nasal mucosa is the prime pathological pathway, such as in treating or relieving nasal congestion. Medicaments that are commonly topically delivered include decongestants, anti-histamines, cromoglycates, steroids and antibiotics. At present, among the known anti-inflammatory pharmaceuticals, topical steroids have been shown to have an effect on nasal congestion. Topical decongestants have also been suggested for use in relieving nasal congestion. The treatment of hypertrophic adenoids and chronic secretory otitis media using topical decongestants, steroids and anti-microbial agents, although somewhat controversial, has also been proposed. Further, the topical administration of pharmaceuticals has been used to treat or at least relieve symptoms of inflammation in the anterior region of the nasopharynx, the paranasal sinuses and the auditory tubes.

Medicaments can also be systemically delivered through the nasal pathway, the nasal pathway offering a good administration route for the systemic delivery of pharmaceuticals, such as hormones, for example, oxytocin and calcitonin, and analgetics, such as anti-migraine compositions, as the high blood flow and large surface area of the nasal mucosa advantageously provides for rapid systemic uptake.

Nasal delivery is also expected to be advantageous for the administration of medicaments requiring a rapid onset of action, for example, analgetics, anti-emetics, insulin, anti-epileptics, sedatives and hypnotica, and other pharmaceuticals, for example, cardio-vascular drugs. It is envisaged that nasal administration will provide for a fast onset of action, at a rate similar to that of injection and at a rate much faster than that of oral administration. Indeed, for the treatment of many acute conditions, nasal administration is advantageous over oral administration, since gastric stasis can further slow the onset of action following oral administration.

It is also expected that nasal delivery could provide an effective delivery route for the administration of proteins and peptides as produced by modern

biotechnological techniques. For such substances, the metabolism in the intestines and the first-pass-effect in the liver represent significant obstacles for reliable and cost-efficient delivery.

Furthermore, it is expected that nasal delivery using the nasal delivery technique of the present invention will prove effective in the treatment of many common neurological diseases, such as Alzheimer's, Parkinson's, psychiatric diseases and intracerebral infections, where not possible using existing techniques. The nasal delivery technique of the present invention allows for delivery to the olfactory region, which region is located in the superior region of the nasal cavities and represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain.

Also, it is expected that the nasal delivery technique of the present invention will allow for the effective delivery of vaccines.

Aside from the delivery of medicaments, the irrigation of the nasal mucosa with liquids, in particular saline solutions, is commonly practised to remove particles and secretions, as well as to improve the mucociliary activity of the nasal mucosa. These solutions can be used in combination with active pharmaceuticals.

To date, nasal medicaments have been primarily delivered as drops or by mechanical nasal spray pumps. With mechanical spray pumps, the mean particle size is typically between 40 µm and 80 µm in order to prevent the inhalation of delivered particles. In general, particles smaller than 10 µm will bypass the nose and can be inhaled. Indeed, the new FDA guidelines require that the fraction of particles less than 10 µm be at most 5 %.

Whilst the provision of a spray having a larger mean particle size prevents the inhalation of the particles, these larger particles are not optimal for achieving a good distribution to the nasal mucosa.

The applicant has now recognized that the closure of the oropharyngeal velum during the delivery of a substance to the nasal airway prevents the possible inhalation of the substance, thereby enabling the delivery of an aerosol having a much smaller mean particle size than achieved by traditional nasal spray pumps. In this way, an aerosol can be generated which has an optimal particle size distribution.

In addition, the applicant has recognized that, by establishing a bi-directional flow through the nasal cavities as described in WO-A-00/51672, that is, an air flow which passes into one nostril, around the posterior margin of the nasal septum and in the opposite direction out of the other nostril, an aerosol having an optimal flow rate and timing can be generated. Furthermore, the bi-directional air flow advantageously acts to stimulate the sensory nerves in the nasal mucosa, thereby conditioning the subject for the delivery and providing a more comfortable delivery situation.

A yet further advantage is that the air flow acts to create a positive pressure inside the nasal passages connected in series, which tends to expand and widen narrow and congested regions.

A still yet further advantage is that the two-point fixation of the device in the nose with a well-fitting nozzle and in the mouth provides a much more stable and reproducible positioning of the device as compared to traditional spray pumps. Thus, in addition to improved deposition and reproducibility, the new concept provides a more user-friendly and intuitive nasal delivery method.

Furthermore, a delivery device, in being pre-primed and actuatable by the oral exhalation breath of a subject, does not require the application of an actuation force by the subject at the time of actuation. Traditionally, mechanical liquid delivery pumps are operated by the manual compression of a chamber containing a volume of liquid to expel a flow of a metered volume of liquid, and mechanical powder delivery pumps are operated by the manual compression of a chamber containing a volume of air to drive

and expel a flow of a metered amount of a dry powder. Such operation requires a relatively high actuation force, typically of the order of 50 N, which high force often leads to significant movement of the delivery device, it being very difficult to maintain a delivery device stationary when attempting to apply a high actuation force. Movement of the delivery device, both in the positioning and orientation of the nozzle, will lead to poor reproducibility, dose accuracy and patient compliance. In being pre-primed and actuatable by the oral exhalation breath of a subject, the delivery device of the present invention overcomes this problem.

In addition, by not requiring a subject to apply an actuation force at the instance of delivery, the delivery device provides for the same actuation force in each delivery, and also provides for delivery at an optimal pressure and/or flow rate, and the delivery of substance having an optimized particle size distribution.

Yet furthermore, in providing for the closure of the oropharyngeal velum of a subject, substance is prevented from entering the lower airway, and also, in a preferred embodiment, bi-directional delivery can be achieved through the nasal cavities.

In one aspect the present invention provides a breath-actuated delivery device, comprising: a delivery unit actuatable to deliver substance on application of a delivery force thereto; a loading unit actuatable to apply the delivery force to the delivery unit to actuate the same; a mouthpiece through which a subject in use exhales; an air channel in fluid communication with the mouthpiece; and an actuating member disposed in the air channel, the actuating member comprising a flexible, bi-stable element actuatable, on exhalation by the subject into the mouthpiece, between a first, non-actuated state and a second, actuated state in which the actuating member actuates the loading unit to apply the delivery force to the delivery unit to actuate the same.

In one embodiment the delivery unit comprises a pump unit.

In one embodiment the pump unit is configured to deliver an aerosol.

In another embodiment the pump unit is configured to deliver a jet.

In one embodiment the substance comprises a liquid.

In another embodiment the substance comprises a powder.

In another embodiment the delivery unit comprises an aerosol canister configured to deliver an aerosol.

In one embodiment the delivery unit comprises a liquid delivery unit.

In another embodiment the delivery unit comprises a powder delivery unit.

In one embodiment the delivery unit is configured to deliver an aerosol.

In another embodiment the delivery unit is configured to deliver a jet.

Preferably, the loading unit comprises a drive member which is actuatable from a loaded position to actuate the delivery unit, a biasing element for loading the drive member with the delivery force, and a restraining member for normally restraining the drive member in the loaded position and being configured to be released on actuation of the actuating member to the actuated state such as to cause the biasing element to drive the drive member to actuate the delivery unit.

In one embodiment the restraining member comprises a tether which is broken on actuation of the actuating member.

In one embodiment the tether comprises at least one filament.

Preferably, the tether comprises a plurality of filaments.

In one embodiment the at least one filament comprises a strand.

In another embodiment the at least one filament comprises a sheet.

Preferably, the at least one filament is formed of a notch-sensitive material.

More preferably, the at least one filament is axially stretched such as to be notch sensitized.

In another embodiment the restraining member comprises a gas support cushion which is vented on actuation of the actuating member.

Preferably, the gas support cushion is ruptured on actuation of the actuating member.

Preferably, the drive member and the restraining member are formed as a single integral unit.

Preferably, the loading unit further comprises a loading member which is operable to load the biasing element with the delivery force.

More preferably, the loading member comprises a loading button which is moved to a loaded position to load the biasing element with the delivery force and configured to be latched in the loaded position.

In one embodiment the bi-stable element of the actuating member has equal bi-stable states.

In another embodiment the bi-stable element of the actuating member has unequal bi-stable states, whereby the actuating force required to switch the bi-stable element to the actuated state is less than the force as would be required to switch the bi-stable element from the actuated state to the non-actuated state.

In one embodiment the actuating member further comprises a releasing element disposed to the bi-stable element thereof which is configured to release the restraining member of the loading unit.

In another embodiment the loading unit further comprises a releasing element which is operative, on actuation of the actuating member to the actuated state, to release the restraining member.

In one embodiment the actuating member is configured such as substantially to close the air channel such that the actuating member is actuated on generation of a predeterminable pressure in the mouthpiece.

In another embodiment the actuating member is configured such as to provide for an air flow through the air channel when in the non-actuated state and close the air channel when in the actuated state.

In a further embodiment the actuating member is configured such as substantially to close the air channel when in the non-actuated state and provide for an air flow through the air channel when in the actuated state.

In a yet further embodiment the actuating member is configured such as to provide for an air flow at a first rate through the air channel when in the non-actuated state and an air flow at a second rate, higher than the first rate, through the air channel when in the actuated state.

Preferably, the delivery device is a nasal delivery device, and further comprising: a nosepiece for fitting to a nostril of the subject through which substance is delivered into the nasal airway of the subject.

More preferably, the nosepiece is in fluid communication with the air channel such that an air flow delivered through the air channel is directed through the nosepiece.

In one embodiment the delivery device further comprises: a pressure-sensitive release mechanism for providing for operation of the actuating member when a sufficient flow cannot be achieved through the nosepiece on exhalation by the subject into the mouthpiece.

In one embodiment the pressure-sensitive release mechanism comprises a valve which is disposed downstream of the air channel and vents the air channel to atmosphere on generation of a predeterminable pressure in the mouthpiece.

In another embodiment the pressure-sensitive release mechanism comprises a flexible diaphragm which is coupled to the actuating member such that generation of a predeterminable pressure in the mouthpiece acts to deflect the diaphragm and actuate the coupled actuating member.

In another aspect the present invention provides a delivery device, comprising: a delivery unit actuatable to deliver substance on application of a delivery force thereto; and a loading unit actuatable to apply the delivery force to the delivery unit to actuate the same, the loading unit comprising a drive member actuatable from a loaded position to actuate the delivery unit, a biasing element for loading the drive member with the delivery force, and a restraining member for normally restraining the drive member in the loaded position and being configured to be broken on actuation of the loading unit to release the drive member and cause the biasing element to drive the drive member to actuate the delivery unit.

In one embodiment the restraining member comprises a tether which is broken on actuation of the actuating member.

In one embodiment the tether comprises at least one filament.

Preferably, the tether comprises a plurality of filaments.

In one embodiment the at least one filament comprises a strand.

In one embodiment the at least one filament comprises a sheet.

Preferably, the at least one filament is formed of a notch-sensitive material.

More preferably, the at least one filament is axially stretched such as to be notch sensitized.

In another embodiment the restraining member comprises a gas support cushion which is ruptured on actuation of the actuating member.

Preferably, the delivery device further comprises: an actuating member actuatable to break the restraining member and actuate the loading unit.

More preferably, the delivery device further comprises: a mouthpiece through which the subject in use exhales; and an air channel in fluid communication with the mouthpiece; and wherein the actuating member is disposed in the air channel such as to be actuated on exhalation by the subject.

Yet more preferably, the actuating member comprises a flexible, bi-stable element actuatable, on exhalation by the subject into the mouthpiece, between a first, non-actuated state and a second, actuated state in which the actuating member actuates the loading unit to apply the delivery force to the delivery unit to actuate the same.

In a further aspect the present invention provides a breath-actuated delivery device, comprising: a mouthpiece through which a subject in use exhales; an air channel in fluid communication with the mouthpiece; and a flexible diaphragm disposed in the air channel, the diaphragm providing for at least a restricted air flow through the air channel until a predeterminable actuation pressure is developed in the mouthpiece, and, on generation of the predeterminable actuation pressure in the mouthpiece, providing for an air flow through the air channel.

Preferably, the diaphragm substantially closes the air channel until the predeterminable actuation pressure is developed in the mouthpiece.

In a preferred embodiment the diaphragm substantially closes the air channel until the predeterminable actuation pressure is developed in the mouthpiece.

Preferably, the delivery device further comprises: a rupturing element for rupturing the diaphragm on generation of the predeterminable actuation pressure in the mouthpiece.

Preferably, the diaphragm is a resilient element.

Preferably, the delivery device is a nasal delivery device, and further comprises: a nosepiece for fitting to a nostril of the subject and through which substance is delivered to the nasal airway of the subject.

More preferably, the nosepiece is in fluid communication with the air channel, and an air flow, when delivered through the air channel, acts to entrain substance.

Preferred embodiments of the present invention will now be described hereinbelow by way of example only with reference to the accompanying drawings, in which:

Figure 1 illustrates a perspective view of a nasal delivery device in accordance with a first embodiment of the present invention;

Figure 2 illustrates a part cut-away perspective view of Figure 1;

Figure 3(a) illustrates a vertical sectional view of the delivery device of Figure 1, where in a first, rest or inoperative configuration;

Figure 3(b) illustrates a vertical sectional view of the delivery device of Figure 1, where in a loaded configuration and with the subject commencing exhalation through the mouthpiece;

Figure 3(c) illustrates a vertical sectional view of the delivery device of Figure 1, where the actuating member of the breath-actuation mechanism is operated by the exhalation of the subject developing an actuation force;

Figure 3(d) illustrates a vertical sectional view of the delivery device of Figure 1, where the delivery unit is actuated to open the substance reservoir thereof;

Figure 3(e) illustrates a vertical sectional view of the delivery device of Figure 1, where the delivery unit is actuated to deliver substance from the nosepiece;

Figure 4(a) illustrates a perspective view of a nasal delivery device as one modification of the first embodiment of the present invention, where the actuating member is in the non-actuated state;

Figure 4(b) illustrates the delivery device of Figure 4(a), where the actuating member is in the actuated state and immediately prior to actuation of the delivery unit;

Figure 5(a) illustrates a perspective view of a nasal delivery device as another modification of the first embodiment of the present invention, in a non-actuated state;

Figure 5(b) illustrates the delivery device of Figure 5(a), in state immediately prior to actuation;

Figure 5(c) illustrates the delivery device of Figure 5(a), in an actuated state; and

Figure 6 schematically illustrates the anatomy of the upper respiratory tract of a human subject.

Figures 1 to 3 illustrate a breath-actuated nasal delivery device in accordance with a first embodiment of the present invention.

The delivery device comprises a body unit 14 which comprises a housing 15, in this embodiment provided by first and second housing parts 15a, 15b, which is typically gripped in the hand of a user, a mouthpiece 17 through which the user exhales to actuate the delivery device, and a nosepiece 19 for fitting to a nostril of the user and through which substance is delivered to the nasal airway of the user.

The housing 15 includes a cavity 21, an inlet passage 23 which is in fluid communication with the cavity 21 and fluidly connected with the mouthpiece 17 such that an air flow developed by the user on exhaling into the mouthpiece 17 is delivered through the inlet passage 23 into the cavity 21, and an outlet passage 25 which is in fluid communication with the cavity 21 and fluidly connected with the nosepiece 19 such that an air flow delivered into the cavity 21 is delivered through the nosepiece 19.

In this embodiment the inlet passage 23 has a narrow, substantially rectangular section, the downstream end of which opens into the cavity 21 in the housing 15.

The housing 15 further includes an aperture 27, in this embodiment in a lower end thereof, in which a loading member 69 for priming the delivery device is disposed, as will be described in more detail hereinbelow.

The housing 15 further includes a latch element 29, in this embodiment a detent, for latching the loading member 69 when in the primed position, again as will be described in more detail hereinbelow.

The housing 15 further includes at least one, in this embodiment a plurality of external venting apertures 30 which provide for a vent from the cavity 21 in the housing 15 to atmosphere. The venting apertures 30 are normally isolated from the atmosphere by a pressure-sensitive release valve 97, as will be described in more detail hereinbelow, and are opened by opening the pressure-sensitive release valve 97 when a sufficient flow rate cannot be developed through the nosepiece 19, for example, as a result of the nasal passage of the user being congested, and the pressure in the cavity 21 in the housing 15 exceeds a predetermined threshold pressure.

In this embodiment the mouthpiece 17 is configured to be gripped in the lips of the user. In an alternative embodiment the mouthpiece 17 could be configured to be gripped by the teeth of the user and sealed by the lips of the user. In a preferred embodiment the mouthpiece 17 is specifically configured to have one or both of a shape and geometry which allows the delivery device to be gripped repeatedly in the same position, thereby providing for the nosepiece 19 to be reliably inserted in the same position in the nasal cavity.

The nosepiece 19 includes a support member 32 which supports the outlet member 39 of a delivery unit 37, as will be described in more detail hereinbelow. The support member 32, in this embodiment an annular member, includes a central, inner aperture 33 in which the nozzle block 41 of the outlet member 39 of the delivery unit 37 is disposed to deliver substance therefrom, and defines at least one, in this embodiment a plurality of outer apertures 35 about the central aperture 33 through which an air flow developed by an exhalation breath of the user is delivered. In this embodiment the outer apertures 35 are configured, here shaped and dimensioned, such as to direct air flows at the delivered substance as delivered from the nozzle outlet 43 of the nozzle block 41 of the outlet member 39, which air flows interact with the delivered substance such as to optimise the delivery characteristics of the delivered substance.

The delivery device further comprises a delivery unit 37, in this embodiment a pump unit, which is actuatable to deliver a metered dose of substance.

The delivery unit 37 comprises an outlet member 39 which is supported, in this embodiment in a fixed position, by the supporting member 32 of the nosepiece 19, and a container member 40 which contains substance to be delivered and is slideably disposed to the outlet member 39 to deliver a metered volume of substance on driving the container member 40 relative to the outlet member 39.

The outlet member 39 comprises a nozzle block 41 at one, the forward, end thereof which includes a nozzle outlet 43 from which substance is delivered, a piston block 45 at the other, rear end thereof, and a hollow needle 47 which extends from the rear end of the piston block 45 and is fluidly connected to the nozzle outlet 43.

In this embodiment the nozzle outlet 43 is configured to deliver an aerosol of fine liquid droplets of substance on actuation of the delivery unit 37. In an alternative embodiment the nozzle outlet 43 could be configured to provide for the delivery of a liquid jet of substance.

The container member 40 comprises a body 49 which includes a cylinder bore 51, in this embodiment having a cylindrical inner peripheral surface, one, the rear, end of which is closed and the other, forward end of which is open and receives the piston block 45 of the outlet member 39, and a seal element 55 which is disposed in sealing engagement with the cylinder bore 51 such as to define an enclosed chamber 57 containing substance within the cylinder bore 51. The seal element 55 is configured to be rupturable by the hollow needle 47 of the outlet member 39, such that, on driving the container member 40 relative to the outlet member 39, the seal element 55 is driven onto the hollow needle 47 such as to be ruptured by the same, with the contained volume of substance in the chamber 57 being substantially incompressible, and, following rupture of the seal element 55 and with continued driving of the container member 40, substance is delivered

through the hollow needle 47 and from the nozzle outlet 43 of the nozzle block 41.

The delivery device further comprises a loading unit 61 which is configured, when actuated, to apply a delivery force to the delivery unit 37, which delivery force is such as to drive the container member 40 of the delivery unit 37 relative to the outlet member 39 of the delivery unit 37, and effect delivery of substance from the nozzle outlet 43 of the nozzle block 41.

The loading unit 61 comprises a drive member 63 which is operative to transmit the delivery force to the delivery unit 37, a restraining member 65 which acts normally to restrain the drive member 63 when loaded by the delivery force and is operable to release the drive member 63, a biasing element 67, in this embodiment a resilient element, here a compression spring, which, when loaded, applies the delivery force to the drive member 63, and a loading member 69 which is operative to load the biasing element 67 to the delivery force. In this embodiment the drive member 63 and the restraining member 65 are formed as a single integral unit.

In this embodiment the drive member 63 comprises a cradle 71 in which the container member 40 of the delivery unit 37 is disposed and an outwardly-directed flange 73 which is engaged by the biasing element 67.

In this embodiment the restraining member 65 comprises a tether 75, one end of which is attached to the cradle 71 of the drive member 63 and the other end of which is attached to the housing 15, such that, on loading the cradle 71 with the delivery force, the tether 75 is tensioned. In this embodiment the tether 75 comprises a single filament which is configured to be cut by a cutter element 93 of an actuating member 89, as will be described in more detail hereinbelow, with the cutting of the tether 75 acting to release the restraining member 65. In another embodiment the tether 75 could comprise a plurality of filaments. In one embodiment each filament could comprise a strand or a sheet.

In this embodiment the restraining member 65 is formed of a plastics material, here Nylon (RTM), and the tether 75 is notch sensitized by axial stretching.

In this embodiment the biasing element 67, as compression spring, is disposed about the tether 75 when in the unloaded state such as to protect the tether 75, and thereby prevent release of the restraining member 65 when in the unloaded state.

In this embodiment the loading member 69 comprises a loading button 79 at one, the lower, end thereof, which is typically loaded by the thumb of the user in loading the biasing element 67, an engagement element 81 at the other, upper end thereof which engages the biasing element 67 to load the same, and a support element 83 which interconnects the loading button 79 and the engagement element 81.

In this embodiment the loading button 79 of the loading member 69 includes a peripheral seal 85 which is configured to seal with the aperture 27 in the housing 15 when in the loaded position, as illustrated in Figure 3(b), such as to prevent the escape therefrom of an air flow as delivered into the cavity 21 in the housing 15.

In this embodiment the engagement element 81 of the loading member 69 includes an outwardly-directed flange 87 which acts to prevent the escape of the loading member 69 from the aperture 27 in the housing 15 when in the unloaded position, as illustrated in Figure 3(a), and engages the latching element 29 on the housing 15 to latch the loading member 69 in the loaded position, as illustrated in Figure 3(b).

The delivery device further comprises a breath-actuated actuating member 89 which is disposed in the inlet passage 23 of the housing 15 and operative, on generation of a predetermined force by the exhalation breath of the user, to release the restraining member 65, and thereby effect actuation of the delivery unit 37.

In this embodiment the actuating member 89 comprises a flexible, bi-stable element 91 which is switched from a first, non-actuated state, as illustrated in Figure 3(a), to a second, actuated state, as illustrated in Figure 3(c), on generation of a predetermined actuating force thereat, in this embodiment through the development of a predetermined exhalation flow rate through the mouthpiece 17, and a cutter element 93 which is fixed to the bi-stable element 91, with the cutter element 93 acting to cut the tether 75 of the restraining member 65.

In this embodiment the bi-stable element 91 comprises an elongate band, in a preferred embodiment of a plastics material, here a thermoplastic elastomer (TPE), which is one or both of shaped and dimensioned relative to the inlet passage 23 in the housing 15 such as, when in the non-actuated state, to allow an air flow at a first predetermined flow rate through the inlet passage 23 on exhalation by the user through the mouthpiece 17, and, when switched to the actuated state, the bi-stable element 91 is moved clear of the inlet passage 23 in the housing 15 and provides for the delivery of an air flow at a second, higher flow rate through the inlet passage 23, and hence the nosepiece 19, which interacts with the delivered substance. In alternative embodiments the bi-stable element 91 can be configured such as to provide alternative flow schemes, for example, in closing the inlet passage 23 in both the non-actuated and actuated states, in closing the inlet passage 23 when in the non-actuated state and providing for an air flow through the inlet passage 23 when in the actuated state, in providing for an air flow through the inlet passage 23 when in the non-actuated state and closing the inlet passage 23 when in the actuated state, and in providing for a uniform flow rate through the inlet passage 23 when in the actuated and non-actuated states.

In this embodiment the delivery device further comprises a pressure-sensitive release valve 97 which acts to provide for a flow through the inlet passage 23 in the housing 15 when the pressure in the cavity 21 in the

housing 15 exceeds a predetermined pressure, as caused by at least partial obstruction of the nasal airway of the user.

Operation of the delivery device will now be described hereinbelow with reference to Figures 3(a) to (e).

The user first primes the delivery device, as illustrated in Figure 3(a), by depressing the loading member 69 until latched in the primed position in the housing 15. In this configuration, the biasing element 67 is biased, here through compression of the compression spring, such as to load the drive member 63 with a predetermined delivery force, with the tether 75 of the restraining mechanism 65 being tensioned by the delivery force.

The user then inserts the nosepiece 19 in one of his/her nostrils, grips the mouthpiece 17 in his/her lips, and commences exhaling through the mouthpiece 17, as illustrated in Figure 3(b). The air flow developed by exhalation through the mouthpiece 17 passes through the cavity 21 in the housing 15 and into the nasal airway of the user through the mouthpiece 17.

In this embodiment the delivery device is configured normally to deliver the exhalation breath through one nostril of the user such as to flow around the posterior margin of the nasal septum and out of the other nostril of the user, thereby achieving bi-directional flow through the nasal cavities as disclosed in WO-A-00/51672.

In exhaling though the mouthpiece 17, the developed air flow applies an actuation force to the bi-stable element 91 of the actuating member 89. On reaching a predetermined flow rate, the actuation force is such as to switch the bi-stable element 91 from the non-actuated state, as illustrated in Figure 3(b), to the actuated state, as illustrated in Figure 3(c).

In being switched to the actuated state, the bi-stable element 91 acts to drive the cutter element 93, which is fixed thereto, to cut the tether 75 of the restraining member 65, which acts to release the drive member 63 to

actuate the delivery unit 37 by driving the container member 40 of the delivery unit 37 relative to the outlet member 39 of the delivery unit 37.

Following release of the drive member 63, in a first phase as illustrated in Figure 3(d), the drive member 63 acts to drive the container member 40 relative to the outlet member 39 such as to cause the hollow needle 47 of the outlet member 39 to rupture the seal element 55 and provide for fluid communication between the chamber 57 of the container member 40 which contains the substance to be delivered and the nozzle outlet 43 of the nozzle block 41 of the outlet member 39.

Following the rupturing of the seal element 55, the drive member 63 acts further to drive the container member 40 relative to the outlet member 39 such as to expel the substance from the chamber 57 of the container member 40 and from the nozzle outlet 43 of the nozzle block 41 of the outlet member 39, in this embodiment as an aerosol of liquid droplets of substance.

Finally, it will be understood that the present invention has been described in its preferred embodiments and can be modified in many different ways without departing from the scope of the invention as defined in the appended claims.

In one alternative embodiment the delivery unit 37 could comprise an aerosol canister, such as used in a pressurized metered dose inhaler (pMDI), for delivering a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing substance, preferably a medicament either as a suspension or a solution.

In another alternative embodiment the delivery unit 37 could comprise a dry powder delivery unit for delivering a metered dose of substance in a dry powder.

In other embodiments the delivery unit 37 could be configured to re-constitute substance on actuation thereof, typically by admixing at least two liquids to provide a re-constituted liquid substance, at least one liquid and at least one powder to provide a re-constituted liquid substance, and at least two powders to provide a re-constituted powder substance.

In yet another alternative embodiment the cutter element 93 could be omitted from the actuating member 89, and instead be disposed to the housing 15 in opposed relation to actuating member 89 such that the actuating member 89 acts to deflect the tether 75 of the restraining member 65 onto the cutter element 93 so as to cut the tether 75.

In still another alternative embodiment the tether 75 of the restraining member 65 could be configured such as to be broken in some other manner. For example, the tether 75 could be formed of a brittle material which has a high tensile strength but a low bending strength, allowing for fracture of the tether 75 by deflection of the tether 75.

In an alternative embodiment the pressure-sensitive release valve 97 could be replaced by a flexible diaphragm, where defining part of the cavity 21 of the housing 15, which is coupled to the actuating member 89. With this configuration, the diaphragm is deflected when the pressure in the cavity 21 in the housing 15 exceeds a predetermined pressure, as caused by at least partial obstruction of the nasal airway of the user, with the deflection of the diaphragm causing actuation of the coupled actuating member 89.

In another alternative embodiment the bi-stable element 91 of the actuating member 89 could close the inlet passage 23 in the housing 15 such as to provide for actuation of the actuating member 89 on generation of a predetermined actuation pressure in the mouthpiece 17.

In still another alternative embodiment, as illustrated in Figures 4(a) and (b), the restraining member 65 could comprise a gas support cushion 99 which is punctured by the cutter element 93 of the actuating member 89 to

actuate the delivery unit 37. The gas support cushion 99, when normally inflated, acts to hold the drive member 63 against the bias of the biasing element 67, and, when punctured, collapses such as to allow the biasing element 67 to drive the drive member 63. In this embodiment the puncturing of the gas support cushion 99 acts advantageously to provide a supplementary gas flow.

In still yet another alternative embodiment, as illustrated in Figures 5(a) to (c), the delivery device comprises a flexible diaphragm 101, here a resilient element, which closes, or at least substantially closes, the flow path from the mouthpiece 17 to the nosepiece 19 and a rupturing element 103 which is operative to rupture the diaphragm 101 where the diaphragm 101 is subjected to a predetermined actuation pressure. With this configuration, exhalation by a user into the mouthpiece 17 acts to bias the diaphragm 101, as illustrated in Figure 5(b), much in the manner of inflating a balloon, and, when the diaphragm 101 is deflected to a predetermined extent, which corresponds to the generation a predetermined pressure upstream of the diaphragm 101, the rupturing element 103 acts to rupture the diaphragm 101, causing the contained pressurized air to be driven out of the nosepiece 19, as illustrated in Figure 5(c). In this embodiment the delivery unit 37 comprises an impregnated structure, typically a porous mat, as impregnated with substance, either as a liquid or a powder, with the sudden burst of air, as generated on rupturing the diaphragm 101, causing substance to be entrained in the air flow and delivered through the nosepiece 19 to the nasal airway of the user. It will be understood that this embodiment has application in relation to any kind of delivery unit 37 which provides for the delivery of substance.

CLAIMS

1. A breath-actuated delivery device, comprising:
a delivery unit actuatable to deliver substance on application of a delivery force thereto;
a loading unit actuatable to apply the delivery force to the delivery unit to actuate the same;
a mouthpiece through which a subject in use exhales;
an air channel in fluid communication with the mouthpiece; and
an actuating member disposed in the air channel, the actuating member comprising a flexible, bi-stable element actuatable, on exhalation by the subject into the mouthpiece, between a first, non-actuated state and a second, actuated state in which the actuating member actuates the loading unit to apply the delivery force to the delivery unit to actuate the same.

2. The delivery device of claim 1, wherein the delivery unit comprises a pump unit.

3. The delivery device of claim 2, wherein the pump unit is configured to deliver an aerosol.

4. The delivery device of claim 2, wherein the pump unit is configured to deliver a jet.

5. The delivery device of any of claims 1 to 4, wherein the substance comprises a liquid.

6. The delivery device of any of claims 1 to 4, wherein the substance comprises a powder.

7. The delivery device of claim 1, wherein the delivery unit comprises an aerosol canister configured to deliver an aerosol.

8. The delivery device of claim 1, wherein the delivery unit comprises a liquid delivery unit.

9. The delivery device of claim 1, wherein the delivery unit comprises a powder delivery unit.

10. The delivery device of claim 8 or 9, wherein the delivery unit is configured to deliver an aerosol.

11. The delivery device of claim 8 or 9, wherein the delivery unit is configured to deliver a jet.

12. The delivery device of any of claims 1 to 11, wherein the loading unit comprises a drive member which is actuatable from a loaded position to actuate the delivery unit, a biasing element for loading the drive member with the delivery force, and a restraining member for normally restraining the drive member in the loaded position and being configured to be released on actuation of the actuating member to the actuated state such as to cause the biasing element to drive the drive member to actuate the delivery unit.

13. The delivery device of claim 12, wherein the restraining member comprises a tether which is broken on actuation of the actuating member.

14. The delivery device of claim 13, wherein the tether comprises at least one filament.

15. The delivery device of claim 14, wherein the tether comprises a plurality of filaments.

16. The delivery device of claim 14 or 15, wherein the at least one filament comprises a strand.

17. The delivery device of claim 14 or 15, wherein the at least one filament comprises a sheet.

18. The delivery device of any of claims 15 to 17, wherein the at least one filament is formed of a notch-sensitive material.

19. The delivery device of claim 18, wherein the at least one filament is axially stretched such as to be notch sensitized.

20. The delivery device of claim 12, wherein the restraining member comprises a gas support cushion which is vented on actuation of the actuating member.

21. The delivery device of claim 20, wherein the gas support cushion is ruptured on actuation of the actuating member.

22. The delivery device of any of claims 12 to 21, wherein the drive member and the restraining member are formed as a single integral unit.

23. The delivery device of any of claims 12 to 22, wherein the loading unit further comprises a loading member which is operable to load the biasing element with the delivery force.

24. The delivery device of claim 23, wherein the loading member comprises a loading button which is moved to a loaded position to load the biasing element with the delivery force and configured to be latched in the loaded position.

25. The delivery device of any of claims 1 to 24, wherein the bi-stable element of the actuating member has equal bi-stable states.

26. The delivery device of any of claims 1 to 24, wherein the bi-stable element of the actuating member has unequal bi-stable states,

whereby the actuating force required to switch the bi-stable element to the actuated state is less than the force as would be required to switch the bi-stable element from the actuated state to the non-actuated state.

27. The delivery device of any of claims 1 to 26, wherein the actuating member further comprises a releasing element disposed to the bi-stable element thereof which is configured to release the restraining member of the loading unit.

28. The delivery device of any of claims 13 to 26 when appendant upon claim 12, wherein the loading unit further comprises a releasing element which is operative, on actuation of the actuating member to the actuated state, to release the restraining member.

29. The delivery device of any of claims to 1 to 28, wherein the actuating member is configured such as substantially to close the air channel such that the actuating member is actuated on generation of a predeterminable pressure in the mouthpiece.

30. The delivery device of any of claims 1 to 28, wherein the actuating member is configured such as to provide for an air flow through the air channel when in the non-actuated state and close the air channel when in the actuated state.

31. The delivery device of any of claims 1 to 28, wherein the actuating member is configured such as substantially to close the air channel when in the non-actuated state and provide for an air flow through the air channel when in the actuated state.

32. The delivery device of any of claims 1 to 28, where the actuating member is configured such as to provide for an air flow at a first rate through the air channel when in the non-actuated state and an air

flow at a second rate, higher than the first rate, through the air channel when in the actuated state.

33. The delivery device of any of claims 1 to 32, wherein the delivery device is a nasal delivery device, and further comprising:
a nosepiece for fitting to a nostril of the subject through which substance is delivered into the nasal airway of the subject.

34. The delivery device of claim 33 when appendant upon any of claims 30 to 32, wherein the nosepiece is in fluid communication with the air channel such that an air flow delivered through the air channel is directed through the nosepiece.

35. The delivery device of claim 34, further comprising:
a pressure-sensitive release mechanism for providing for operation of the actuating member when a sufficient flow cannot be achieved through the nosepiece on exhalation by the subject into the mouthpiece.

36. The delivery device of claim 35, wherein the pressure-sensitive release mechanism comprises a valve which is disposed downstream of the air channel and vents the air channel to atmosphere on generation of a predeterminable pressure in the mouthpiece.

37. The delivery device of claim 35, wherein the pressure-sensitive release mechanism comprises a flexible diaphragm which is coupled to the actuating member such that generation of a predeterminable pressure in the mouthpiece acts to deflect the diaphragm and actuate the coupled actuating member.

38. A delivery device, comprising:
a delivery unit actuatable to deliver substance on application of a delivery force thereto; and

a loading unit actuatable to apply the delivery force to the delivery unit to actuate the same, the loading unit comprising a drive member actuatable from a loaded position to actuate the delivery unit, a biasing element for loading the drive member with the delivery force, and a restraining member for normally restraining the drive member in the loaded position and being configured to be broken on actuation of the loading unit to release the drive member and cause the biasing element to drive the drive member to actuate the delivery unit.

39. The delivery device of claim 38, wherein the restraining member comprises a tether which is broken on actuation of the actuating member.

40. The delivery device of claim 39, wherein the tether comprises at least one filament.

41. The delivery device of claim 40, wherein the tether comprises a plurality of filaments.

42. The delivery device of claim 40 or 41, wherein the at least one filament comprises a strand.

43. The delivery device of claim 40 or 41, wherein the at least one filament comprises a sheet.

44. The delivery device of any of claims 40 to 43, wherein the at least one filament is formed of a notch-sensitive material.

45. The delivery device of claim 44, wherein the at least one filament is axially stretched such as to be notch sensitized.

46. The delivery device of claim 38, wherein the restraining member comprises a gas support cushion which is ruptured on actuation of the actuating member.

47. The delivery device of any of claims 38 to 46, further comprising:
an actuating member actuatable to break the restraining member and actuate the loading unit.

48. The delivery device of claim 47, further comprising:
a mouthpiece through which the subject in use exhales; and
an air channel in fluid communication with the mouthpiece; and
wherein the actuating member is disposed in the air channel such as to be actuated on exhalation by the subject.

49. The delivery device of claim 48, wherein the actuating member comprises a flexible, bi-stable element actuatable, on exhalation by the subject into the mouthpiece, between a first, non-actuated state and a second, actuated state in which the actuating member actuates the loading unit to apply the delivery force to the delivery unit to actuate the same.

50. A breath-actuated delivery device, comprising:
a mouthpiece through which a subject in use exhales;
an air channel in fluid communication with the mouthpiece; and
a flexible diaphragm disposed in the air channel, the diaphragm providing for at least a restricted air flow through the air channel until a predeterminable actuation pressure is developed in the mouthpiece, and, on generation of the predeterminable actuation pressure in the mouthpiece, providing for an air flow through the air channel.

51. The delivery device of claim 50, wherein the diaphragm substantially closes the air channel until the predeterminable actuation pressure is developed in the mouthpiece.

52. The delivery device of claim 50 or 51, further comprising:
a rupturing element for rupturing the diaphragm on generation of the predeterminable actuation pressure in the mouthpiece.

53. The delivery device of any of claims 50 to 52, wherein the diaphragm is a resilient element.

54. The delivery device of any of claims 50 to 53, wherein the delivery device is a nasal delivery device, and further comprising:
a nosepiece for fitting to a nostril of the subject and through which substance is delivered to the nasal airway of the subject.

55. The delivery device of claim 54, wherein the nosepiece is in fluid communication with the air channel, and an air flow, when delivered through the air channel, acts to entrain substance.

56. A delivery device substantially as hereinbefore described with reference to any of Figures 1 to 3, Figure 4 or Figure 5 of the accompanying drawings.

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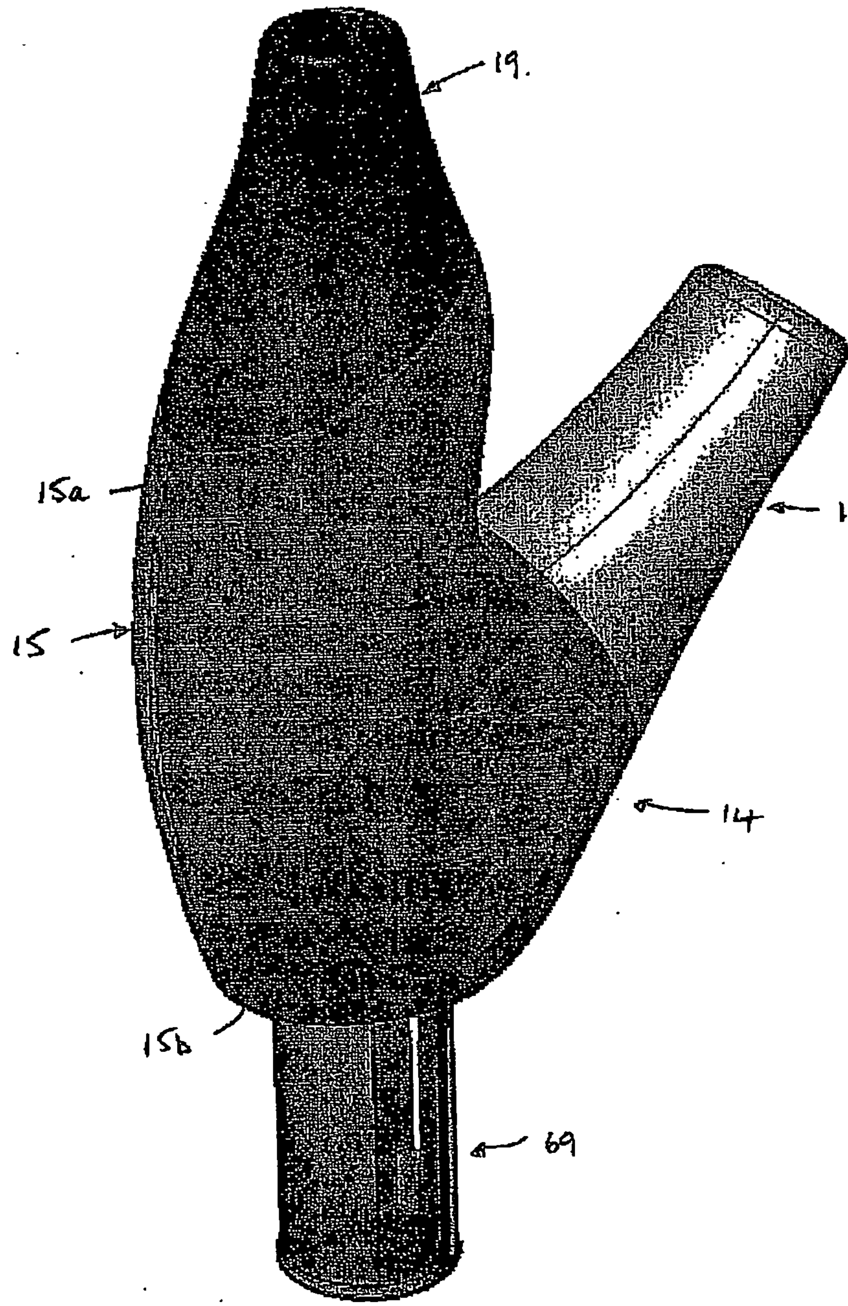

Fig. 1

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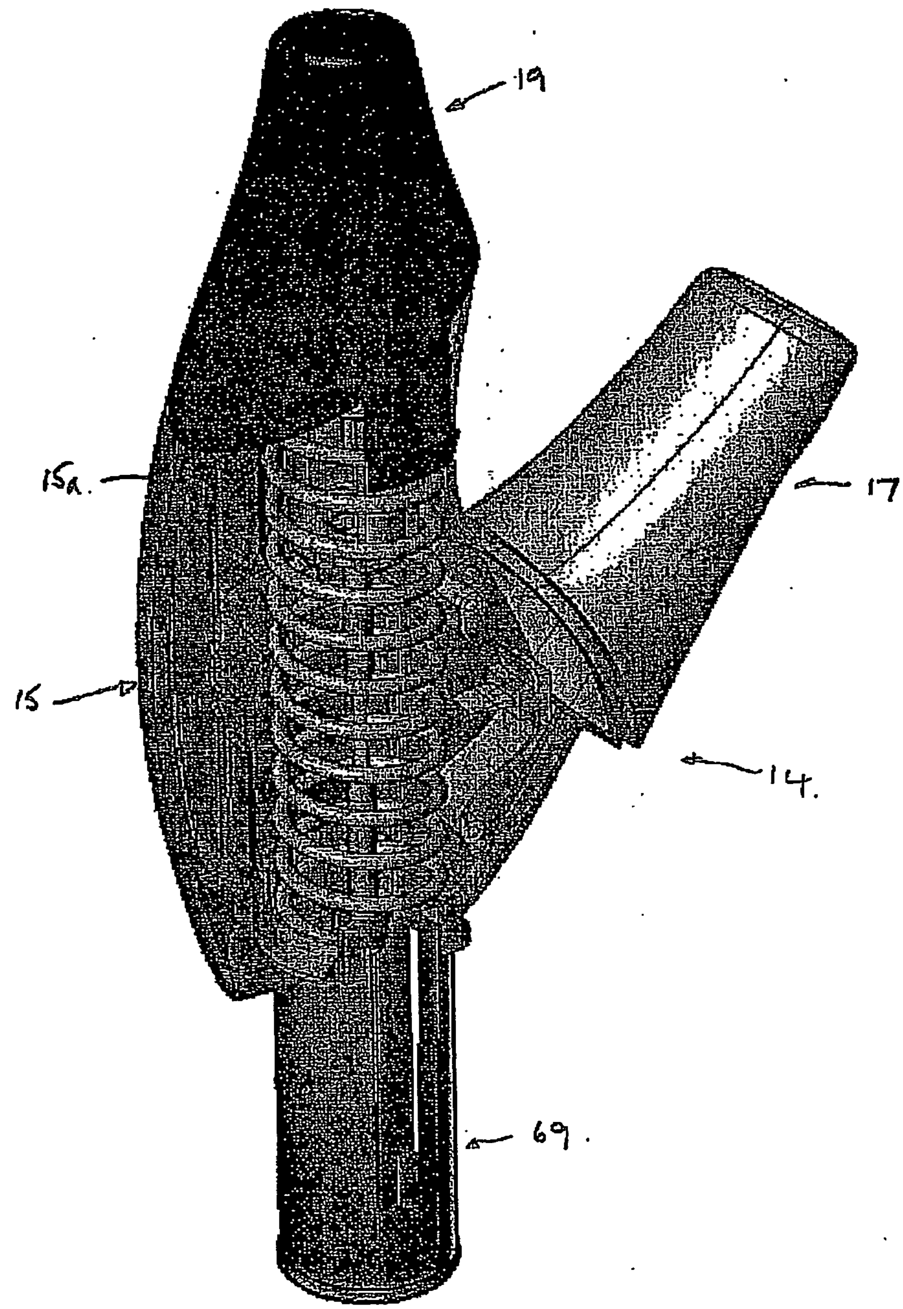

Fig. 2

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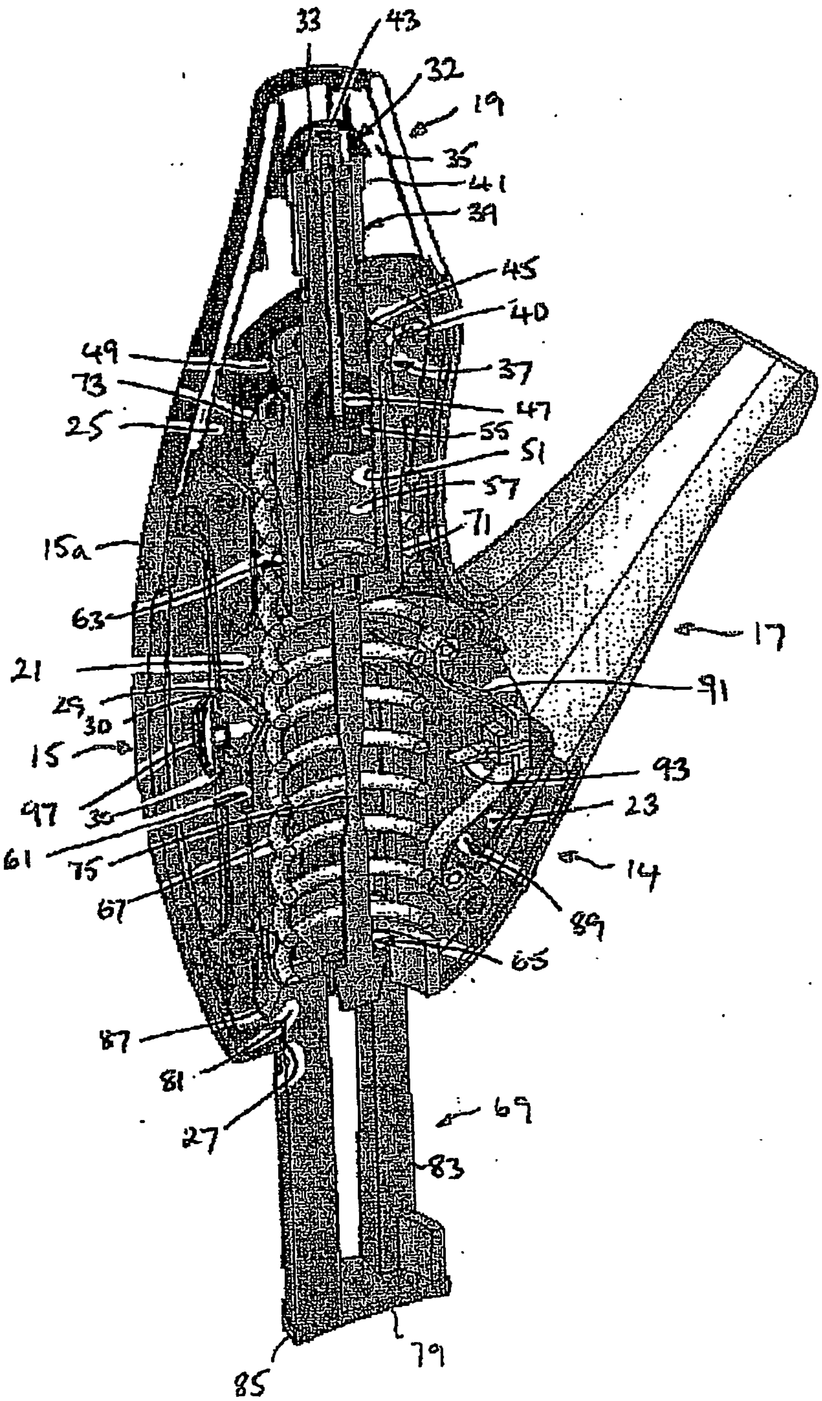
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Fig. 3(a)

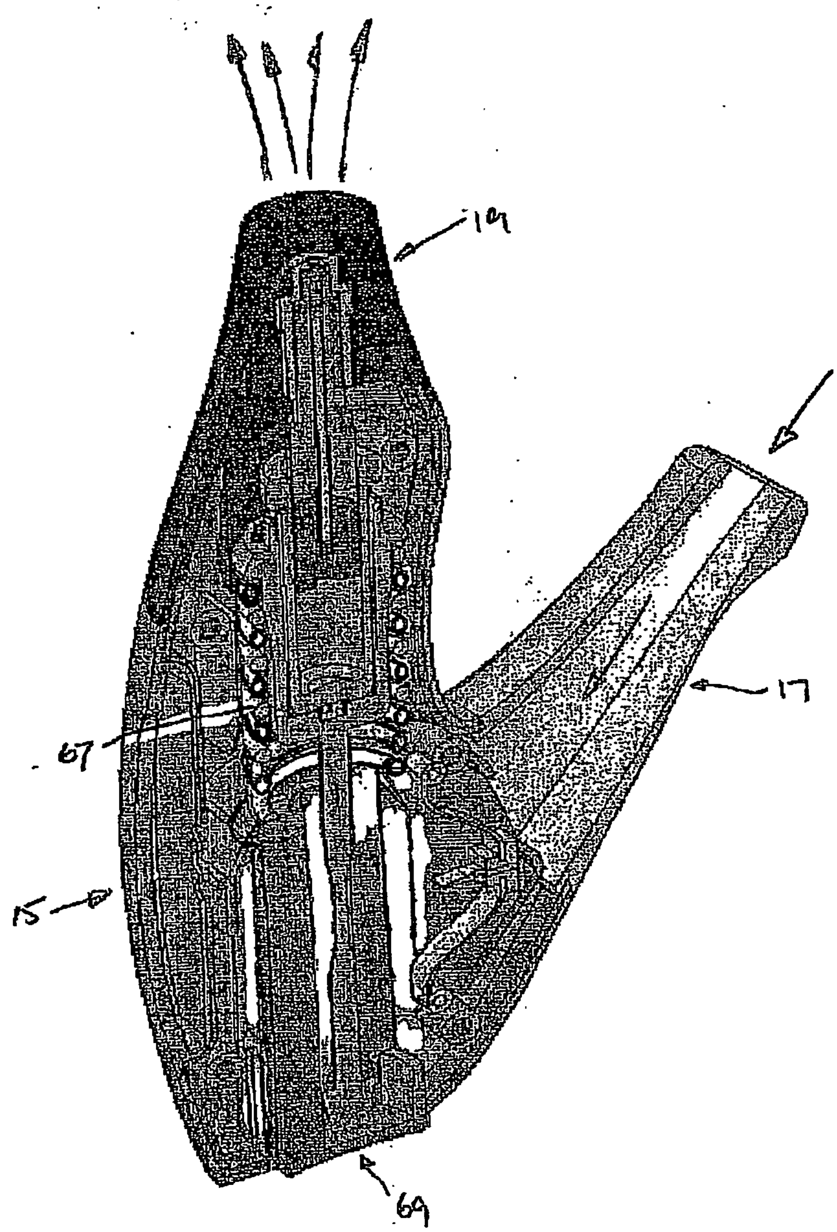

fig. 3(b)

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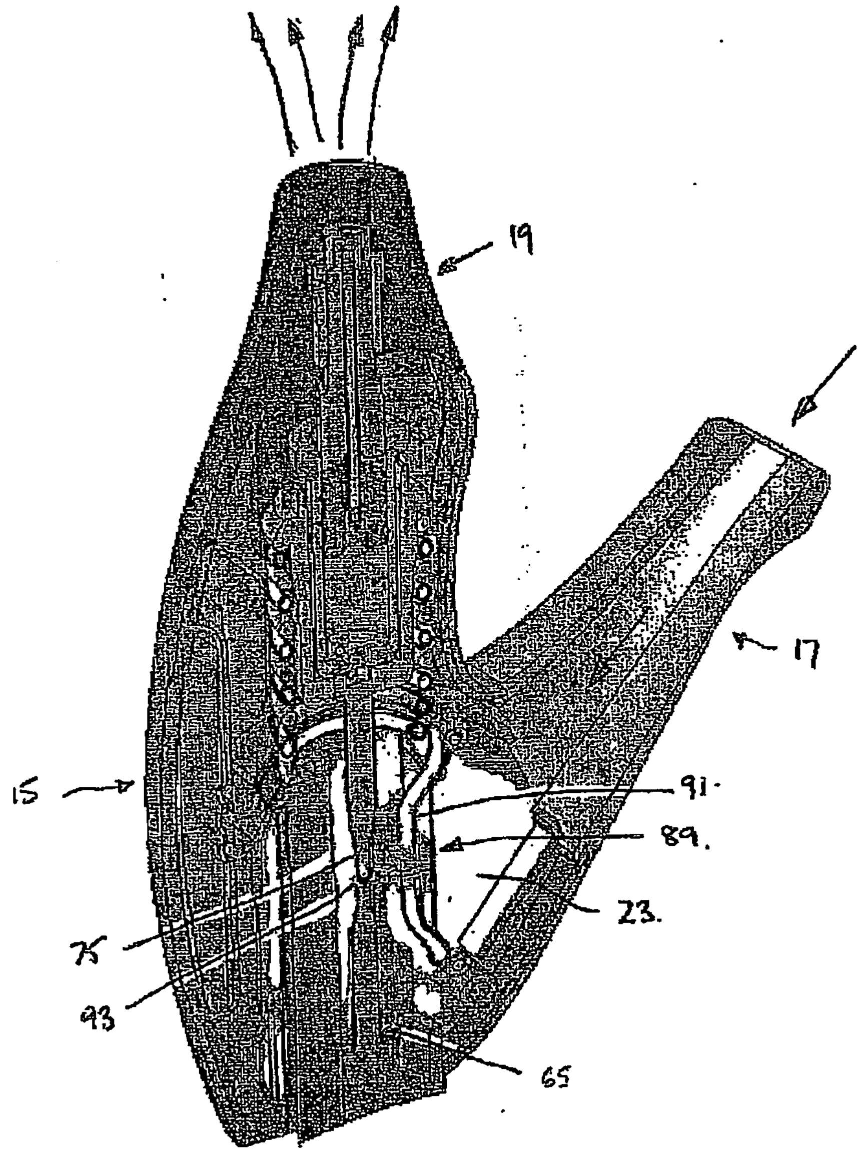

Fig. 3(c)

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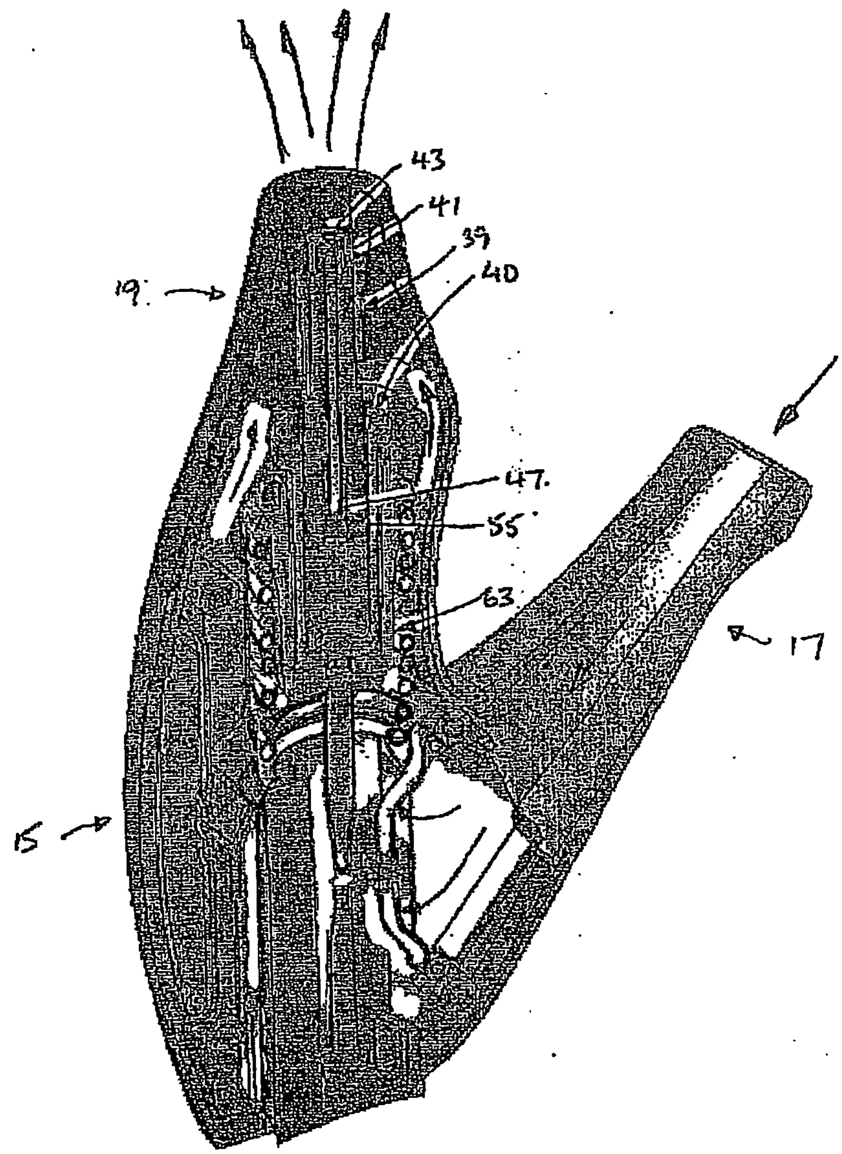

Fig. 3(d)

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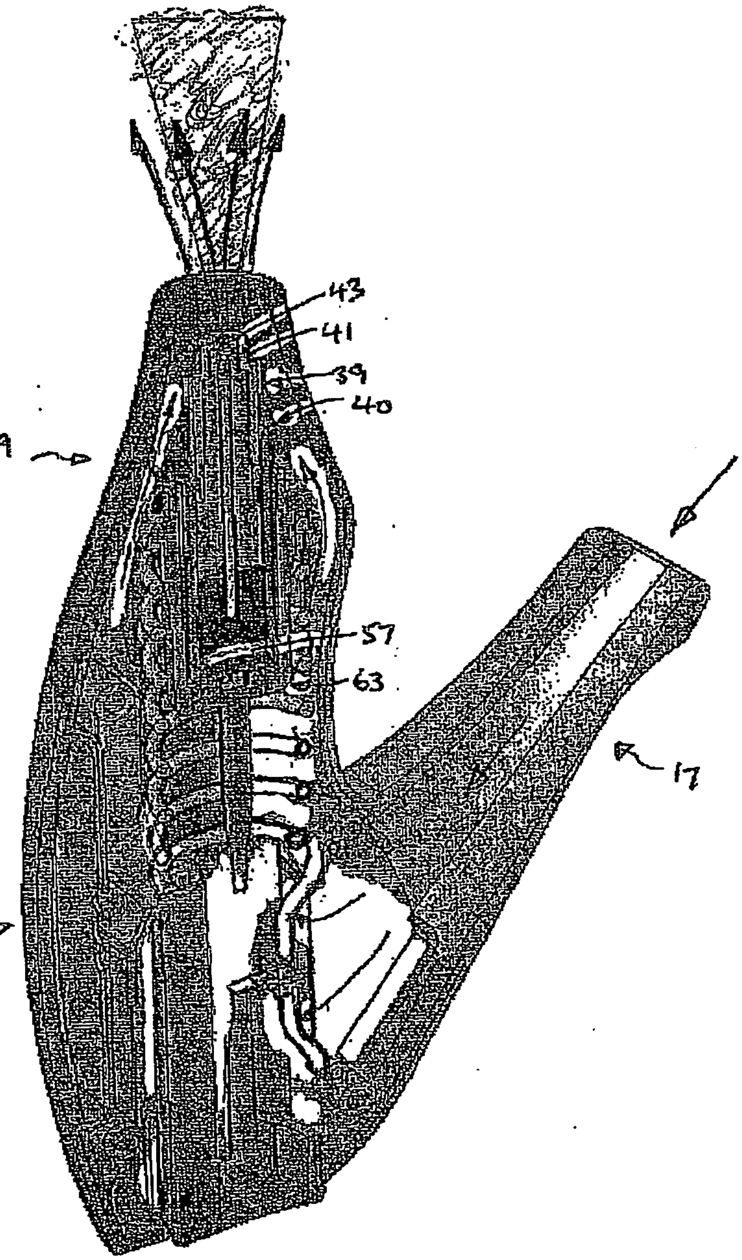

Fig. 3(e)

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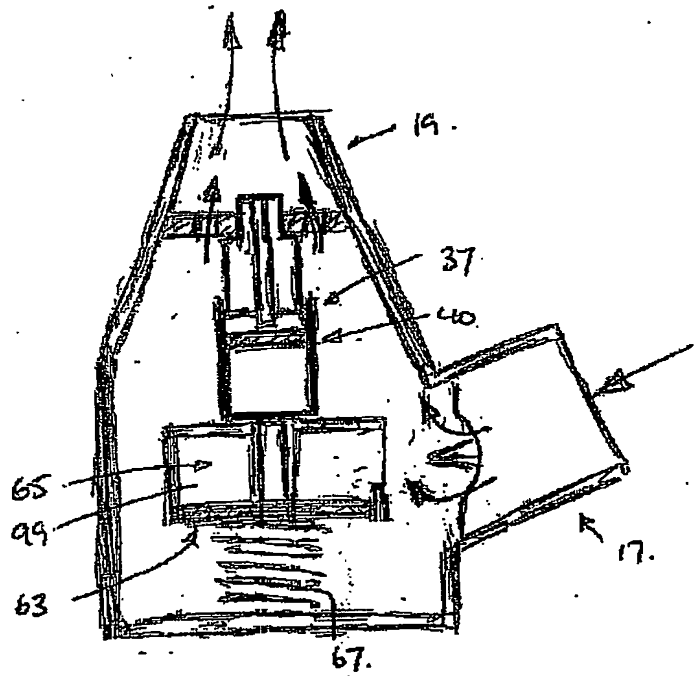

Fig. 4(a)

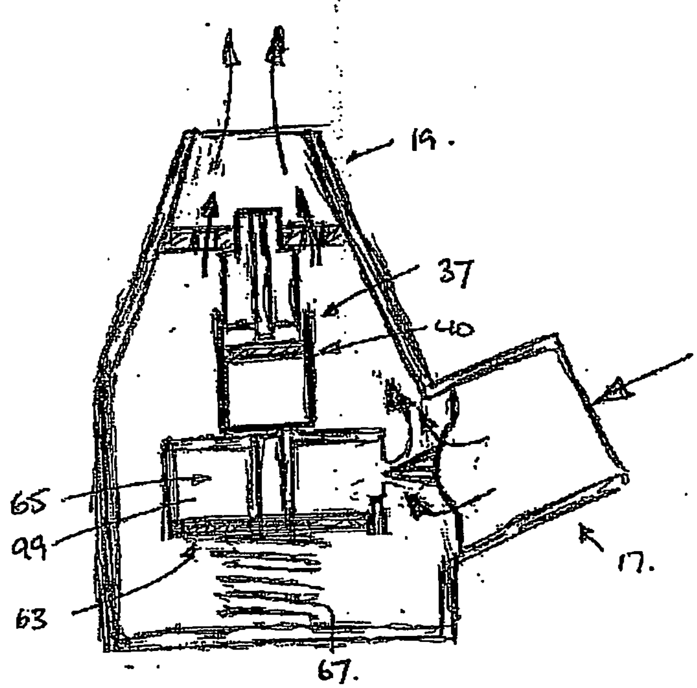

Fig. 4(b)

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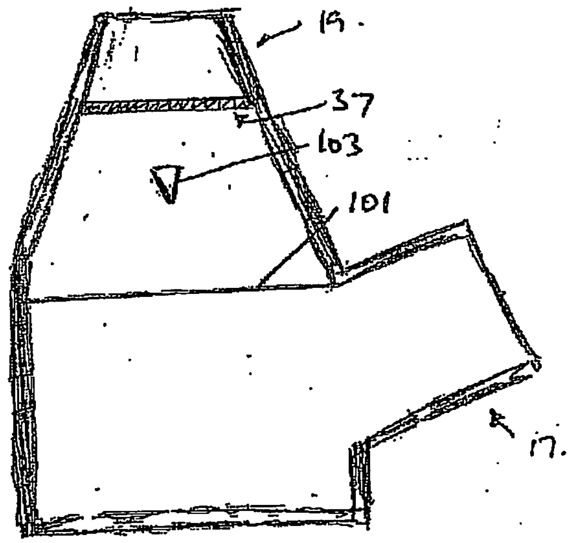

Fig. 5(a)

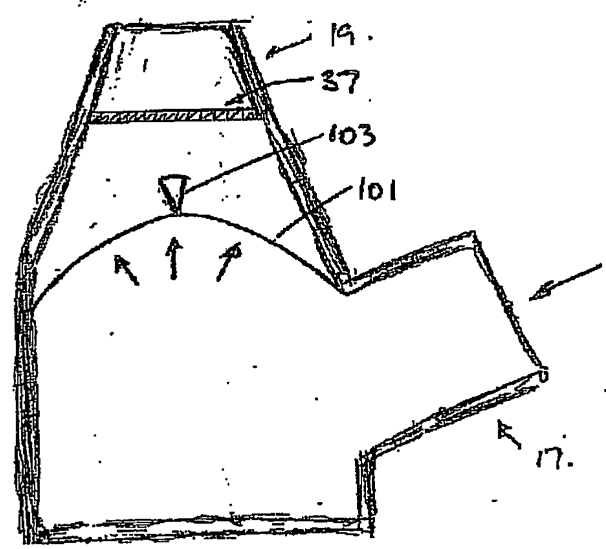

Fig. 5(b)

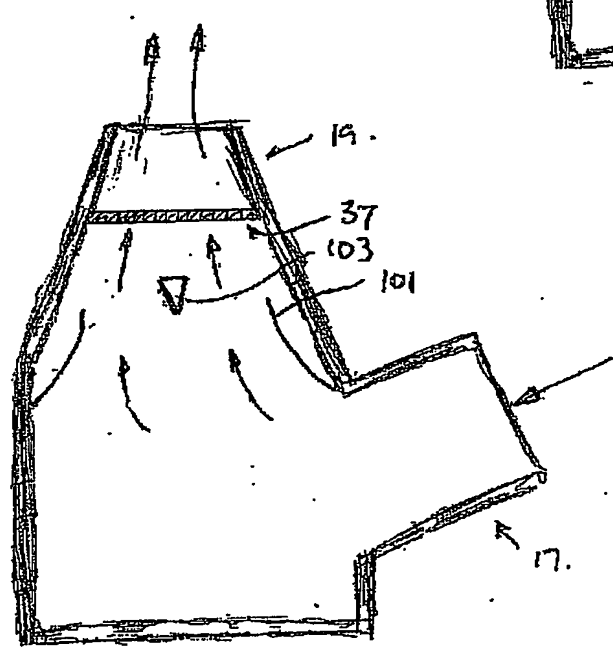

Fig. 5(c)

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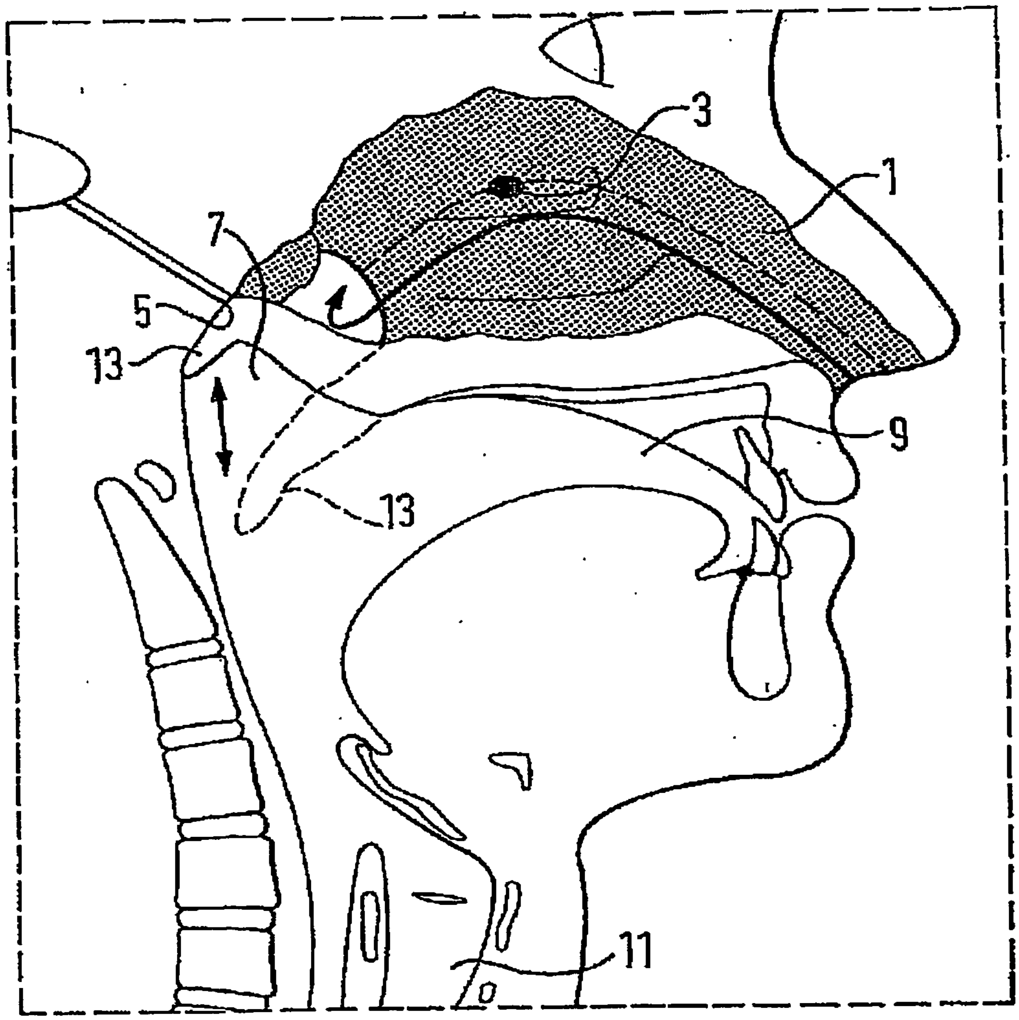

Fig. 6

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